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Browdy and Neimark, PLLC
1625 K Street, N.W.
Suite 1100
Washington, DC 20006

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BALLARD, KIMBERLY	

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/441,140
Filing Date: November 16, 1999
Appellant(s): SOLOMON, BEKA

Roger L. Browdy
For Appellant

EXAMINER'S ANSWER

It is noted that the instant application is a reissue application.

This is in response to the appeal brief filed 10 November 2010 appealing from the Office action mailed 10 December 2009.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 177 and 210-228 are pending in the present application. Claims 177, 210-223 and 225-227 are rejected and are the subject of this appeal.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

Bacskai B.J. et al. "Imaging of Amyloid-β Deposits in Brains of Living Mice Permits Direct Observation of Clearance of Plaques with Immunotherapy", *Nature Medicine*, vol. 7 (2001). pp. 369-372.

Bickel, U. et al. "Development an *in vitro* Characterization of a Cationized Monoclonal Antibody Against βA4 Protein: A Potential Probe for Alzheimer's Disease" *Bioconjugate Chem.*, vol. 5 (Mar/Apr 1994), pp. 119-125.

Hanan, E. & Solomon, B. "Inhibitory Effect of Monoclonal Antibodies on Alzheimer's β-Amyloid Peptide Aggregation", *Amyloid: Int. J. Exp. Clin. Invest.*, vol. 3 (1996), pp. 130-133.

Solomon, B. et al. "Monoclonal Antibodies Inhibit *in vitro* Fibrillar Aggregation of the Alzheimer β-Amyloid Peptide" *Proc. Natl. Acad. Sci. USA*, vol. 94 (1997), pp. 4109-4112.

Walker L.C. et al. "Labeling of Cerebral Amyloid *in vivo* with a Monoclonal Antibody", *J. Neuropathol. Exp. Neurol.*, vol. 53, no. 4 (1994), pp. 377-383.

4,946,778	Ladner et al.	8-1990
EP 0613007 A2	Becker et al.	2-1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

i) The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 177 and 210-218 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claims recite a therapeutic composition comprising a genetically-engineered antibody that inhibits aggregation of β-amyloid or maintains the solubility of soluble beta-amyloid *to an extent at least as great as that obtainable with antibody AMY-33* (emphasis added), or a fragment of said antibody that inhibits aggregation of β-amyloid

or maintains the solubility of soluble beta-amyloid *to an extent at least as great as that obtainable with antibody AMY-33*, and is obtainable using a peptide consisting of residues 1-28 of beta-amyloid as an immunogen. Such would imply the use and possession not only of antibodies have anti-aggregating abilities the same as that of the monoclonal antibody (mAb) AMY-33, but also of antibodies having anti-aggregating properties exceeding that of AMY-33 to any extent. There is no *verbatim* support in the specification as originally filed for anti-β-amyloid antibodies which inhibit aggregation of β-amyloid to a particular specified degree, nor does this language flow naturally from the disclosure as originally filed. Such antibodies having a specific degree of activity represent a genus of antibodies for which Appellant has only demonstrated one species, AMY-33, within the genus. The specification as filed thus does not support the genus of antibodies that is described in terms of meeting or exceeding the ability of the antibody AMY-33 to inhibit β-amyloid aggregation. Similarly, there is no support in the specification as originally filed for a method of making a therapeutic composition comprising an antibody comprising a method step wherein the antibody is screened for having activity at least as great as that obtainable with AMY-33. In order to have such a genus of antibodies, one would have to test the anti-aggregating abilities of candidate antibodies and compare them directly to that of AMY-33. No such assay is implied within the specification.

While the instant specification as originally filed may generically support antibodies that inhibit protein aggregation and the specific “preferred” embodiment of the anti-β-amyloid antibody AMY-33, it does not reasonably provide support for the

genus of antibodies exceeding the anti-aggregating capacity of AMY-33. While a claimed invention is certainly not limited to preferred embodiments, which are typically the embodiments best disclosed and supported by the specification, the claimed invention must be adequately described by the specification as filed. Otherwise, this would be akin to saying that had the Wright brothers filed a patent application disclosing their flying machine, this would provide adequate written description for later claiming a genus of aircraft capable of flying at least as well as their own aircraft that included jet planes and space shuttles. Therefore, the recitation of a single species, AMY-33, does not support the recited genus of antibody molecules as currently amended and claimed.

ii) Claims 177 and 210-218 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 177 and 210-218 are drawn to compositions and methods of making such compositions comprising a genus of genetically-engineered antibody molecules, including both antibodies and fragments thereof, having a specific functional property, and for which Appellant has only disclosed a single species within the genus. For example, the recitation of an antibody capable of inhibiting aggregation of soluble β-amyloid in a subject “to an extent at least as great as that obtainable with antibody

AMY-33" does not meet the written description provision of 35 U.S.C. 112, first paragraph, because there is insufficient guidance and direction for the genus of antibodies broadly encompassed by the claimed invention. The phrase "genetically-engineered antibodies" is given its broadest reasonable interpretation; specifically, it is not limited to single-chain antibodies, but instead broadly encompasses humanized, chimeric, veneered, resurfaced, CDR-grafted and other such engineered antibodies. Because the claims recite the broadly encompassing genus of genetically-engineered antibodies and human monoclonal antibodies, they are considered genus claims. Even with respect to claims 177 (limited to single chain antibodies) and 212-213 (drawn to human monoclonal antibodies), the claims encompass a genus of antibody molecules differing in structure.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are a recitation of the desired inhibitory functional property, a generic binding recitation, and the immunogenic peptide fragment used to obtain the monoclonal antibody from which the claimed genetically-engineered antibody is derived. However, these functional properties and product-by-process limitation (i.e., the genetically-engineered antibody is obtained by genetically engineering the DNA encoding a monoclonal antibody that binds beta-amyloid and "is obtainable using a

immunogen consisting of a peptide consisting of residues 1-28 of beta-amyloid") does not serve to limit the antibody's structure. There is no indication of the particular structural or physical properties of the claimed antibodies, or of any structure/function correlation for antibodies capable of inhibiting beta-amyloid aggregation. Distinguishing structural characteristics that could help to identify members of the claimed genus of antibodies are lacking from the instant specification. And apart from a method step to select for antibodies displaying the particular desired functional characteristics, there is no indication of any specific structural properties required for making the claimed genetically-engineered antibody.

The first paragraph of 35 U.S.C. § 112 "requires a 'written description of the invention' which is separate and distinct from the enablement requirement." *Vas-Cath Inc. v. Mahurkar,* 935 F.2d 1555, 1563 (Fed. Cir. 1991). An adequate written description of a chemical invention "requires a precise definition, such as by structure, formula, chemical name, or physical properties." *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.,* 119 F.3d 1559, 1566 (Fed. Cir. 1997); *Fiers v. Revel,* 984 F.2d 1164, 1171 (Fed. Cir. 1993). "A description of what a material does, rather than of what it is, usually does not suffice." *Rochester,* 358 F.3d at 923; *Eli Lilly,* 119 F.3d at 1568. Instead, the "disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Id.* However, not all functional descriptions "necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is

sufficiently correlated to a particular, known structure." *Amgen Inc. v. Hoechst Marion Roussel, Inc.,* 314 F.3d 1313, 1332 (Fed. Cir. 2003).

In addition, possession of a genus "may be achieved by means of a recitation of a representative number of [compounds]... falling within the scope of the genus." *Eli Lilly,* 119 F.3d at 1569. Possession may not be shown by merely describing how to obtain possession of members of the claimed genus. *See Rochester, supra,* 358.
In this case, there is no description in the instant application nor commonly available in the prior art to sufficiently correlate the desired function – that of inhibiting the aggregation of beta-amyloid, maintaining the solubility of soluble beta-amyloid, or recognizing an epitope within residues 1-28 of beta-amyloid - with that of a particular, known structure. The specification discloses only one mouse monoclonal antibody, AMY-33, which was purchased from ZYMED, San Fransciso, CA, USA (see column 12, lines 4-5), and discusses how to select for and make anti-aggregation molecules such as a monoclonal antibody, a single chain monoclonal antibody, a genetically-engineered monoclonal antibody fragment, or a peptide which mimics the binding site of an antibody. There is no description in the claims or in the specification of other species of molecules to support the broad genus of genetically-engineered antibodies. The skilled artisan cannot envision the detailed chemical structure of the encompassed genetically-engineered inhibitory antibodies having a particular degree of anti-aggregating function, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of selection, isolation, and/or production. Adequate written description requires more than a mere statement that it is

part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel,* 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016. As noted previously, possession may not be shown by merely describing how to obtain possession of members of the claimed genus. *University of Rochester v. G.D. Searle & Co., Inc.,* 358 F.3d 916, 927 (Fed. Cir. 2004); *Regents of the Univ. of Cal. v. Eli Lilly & Co., Inc.,* 119 F.3d 1559, 1566 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed."* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). The instant specification discloses only one purchased monoclonal antibody, AMY-33, inherently capable of meeting the functional inhibitory requirements of the claims and then describes how to make engineered antibody fragments from this selected antibody. No actual genetically-engineered antibodies or engineered antibody fragments of the selected monoclonal antibodies are disclosed.

Therefore, the full breadth of the claims does not meet the written description provision of 35 U.S.C. § 112, first paragraph.

iii) The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 177, 210-213 and 215-217 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bickel et al. (*Bioconjugate Chem*. 1994, 5(2):119-125), as evidenced by Solomon (*Expert Opin Biol Ther*. 2002, 2(8): 907-917), and in view of EP 0613 007 A2 to Becker et al. (published 08/31/1994) and US Patent No. 4,946,778 to Ladner et al. (issued August 7, 1990).

The claims recite a therapeutic composition comprising a pharmaceutical formulation comprising a pharmaceutically acceptable carrier and a genetically-engineered antibody or fragment thereof, wherein the antibody is obtained by genetically-engineering the DNA encoding a monoclonal antibody that inhibits aggregation of beta-amyloid or maintains the solubility of beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33 and is obtainable using a peptide consisting of β-amyloid 1-28 or recognizes an epitope within residues 1-28 of β-amyloid, and wherein said antibody or fragment is not conjugated with a detectable moiety. Dependent claims recite that the β-amyloid is human β-amyloid and that the genetically-engineered monoclonal antibody is a single chain antibody.

Bickel et al. teach that vascular amyloid deposits and senile plaques are among the neuropathologic hallmarks of Alzheimer's disease, wherein the main constituent of

these plaques is β-amyloid protein (see p. 119, left column). Because of the general impermeability of the blood-brain barrier (BBB) to immunoglobulin (IgG), Bickel proposes a delivery strategy involving cationization of IgG in order to use monoclonal antibodies as diagnostic or therapeutic agents in the brain (see abstract). Bickel teaches the development and characterization of a monoclonal antibody, AMY-33, which was produced by immunizing animals with residues 1-28 of human β-amyloid (see p. 122, 1st paragraph under Discussion). AMY-33 is taught to specifically recognize and bind to residues 1-28 of human β-amyloid (see Figure 2 on p. 122), and cationized AMY-33 is demonstrated to retain its binding affinity for β-amyloid and bind to amyloid deposits in brain sections taken from AD patients (see p. 122, 1st column and Figure 3 on p. 123).

In addition to suggesting that highly specific anti-β-amyloid monoclonal antibodies could be used for *in vivo* diagnostic methods that would be expected to be more specific and sensitive for Alzheimer's disease (AD) than clinical criteria (see p. 119), such as for detecting cerebral β-amyloid deposits *in vivo* in the brains of patients with AD (see Abstract), Bickel generally suggests the use of monoclonal antibodies for therapeutic use. For example, Bickel discusses a need for reducing the immunogenicity of cationized antibodies, such as by humanization of murine monoclonal antibodies prior to cationization, so as to facilitate their use of as neurodiagnostic or therapeutic agents in humans (see p. 124, 2nd column).

While the claimed antibody recites functional properties including inhibition of aggregation of β-amyloid and/or maintaining the solubility of soluble β-amyloid, it is

noted that the AMY-33 monoclonal antibody taught by Bickel et al. is the same as that described in the instant specification as possessing such functional characteristics. Additionally, the examiner notes that antibodies raised against the N-terminus of β-amyloid (i.e., Aβ 1-28) intrinsically have "chaperone" or anti-aggregating properties, including solubilization of existing β-amyloid aggregates and inhibition of β-amyloid aggregation, as evidenced by Solomon (see p. 909).

Thus while Bickel et al. teach a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a monoclonal antibody obtainable using β-amyloid 1-28 as a peptide immunogen, wherein the antibody (AMY-33) is evidenced as being capable of inhibiting the aggregation of β-amyloid or maintaining the solubility of soluble β-amyloid by Solomon, Bickel does not teach a genetically-modified antibody that is obtained by genetically engineering the DNA encoding the monoclonal antibody, or that the genetically-engineered antibody is a single-chain antibody. Because the antibody disclosed by Bickel is AMY-33, antibodies engineered from AMY-33 would reasonably be expected to meet the functional limitation that the inhibition of β-amyloid aggregation is "at least as great as that obtainable with antibody AMY-33".

Consistent with the teachings of Bickel, Becker et al. note that Alzheimer's disease is characterized by amyloid plaques and neurofibrillary tangles, wherein β-amyloid peptide again is noted to be the major component of amyloid plaque deposits (see column 1). Becker also notes that β-amyloid peptide can be neurotoxic to neurons (see column 1, lines 30-46). Becker therefore suggests that inhibition of β-amyloid-mediated neurotoxicity would be therapeutically beneficial for the treatment of

Alzheimer's disease, and describes assays that can be used for determining appropriate inhibitors, such as anti-β-amyloid antibodies. Pharmaceutical formulations comprising a pharmaceutically acceptable carrier and an anti-β-amyloid antibody are taught at column 8, lines 19-26 and 31-42, such as for use in the diagnosis and treatment of Alzheimer's disease (column 7, lines 39-52 and column 8, lines16-18). Monoclonal antibodies derived from various species, including humans, are disclosed at column 6, lines 10-19. Thus, Becker teaches the use of anti-β-amyloid human monoclonal antibodies. Becker discloses that the greatest deterrence to the clinical use of antibodies produced in non-human species is the risk of hyperimmunogenicity in human subjects due to the presence of non-human constant regions within the antibodies. Therefore, genetically engineering the DNA encoding the antibodies such that the antibodies retain epitope specificity but reduce immunogenicity is desirable (column 6 lines 31-40). Further, Becker teaches single chain antibodies as another genetically engineered antibody for retaining the binding characteristics of the parental antibody while affording a less immunogenic format (column 7, lines 11-25). Because a single-chain antibody is a genetically-engineered antibody that is obtained by genetically engineering the DNA encoding a monoclonal antibody, as indicated in the instant claims, the limitations regarding “genetically-engineered” have been met.

Ladner et al. also teach the production of single chain antibodies and disclose that they may be used for essentially any purpose that the prior art has envisioned for monoclonal or polyclonal antibodies (column 3, lines 29-31). Ladner discloses, for example, that single chain antibodies may be used in diagnostics, therapy, *in vivo* and

in vitro imaging, purification and biosensor applications (column 3, lines 18-24). Ladner teaches the advantages of single chain antibodies include smaller size, greater stability, reduced cost of production, and greater ease of genetic modifications to improve binding affinity and specificity (column 3, lines 33-48). Ladner also notes that because of the smaller size, single chain antibodies may reduce immunogenicity and thus increase the safety and efficacy of therapeutic applications (column 3, lines 35-38). Ladner further teaches that the single chain antibody "can be utilized by itself, in detectably labeled form, in immobilized form, or conjugated to drugs or other appropriate therapeutic agents, in diagnostic, imaging, biosensors, purifications, and therapeutic uses and compositions. Essentially all uses envisioned for antibodies or for variable region fragments thereof can be considered for the molecules of the present invention." (emphasis added) See column 11, lines 27-34.

Upon reading the teachings of Bickel et al., the skilled artisan would have recognized the desirability of developing improved, less-immunogenic compositions comprising the AMY-33 antibody for the *in vivo* diagnosis or therapy of Alzheimer's disease, particularly in view of Becker's disclosure teaching the use of anti-Aβ antibodies for use in diagnostic and therapeutic applications. While diagnostic use of the AMY-33 antibody is one utility suggested by Bickel, Bickel also suggests that humanized monoclonal antibodies, or antibodies having reduced immunogenicity, could be used therapeutically. Similarly, Becker teaches therapeutic use of less immunogenic molecules, such as anti-Aβ human monoclonal antibodies and single chain antibodies, and Ladner extols the benefits of using single-chain antibodies for therapeutic purposes

as noted above. In fact, Ladner teaches that single chain antibodies may be used for any purpose envisioned by antibodies, and that the single chain antibody may also be used by itself (i.e., unconjugated to a detectable moiety) in therapeutic uses and compositions. Therapeutic use of such antibodies would not require conjugation to a detectable moiety.

Therefore, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to genetically-engineer the monoclonal antibody taught by Bickel et al. to make a single-chain antibody, as taught by Becker and Ladner, with a reasonable expectation of success in producing a molecule with reduced immunogenicity, improved affinity and sensitivity, greater stability, and reduced cost of production compared to whole antibodies. Similarly, it would have been obvious to make a human monoclonal anti-Aβ antibody, as taught by Becker, obtainable using a peptide consisting of residues 1-28 of Aβ because this was the immunogen used to produce the AMY-33 antibody and commonly known and used in the art at the time of filing, and Bickel demonstrates that this antibody binds specifically to brain amyloid deposits, thus evidencing the usefulness of antibodies obtained with this immunogen. Human monoclonal antibodies were known to be less immunogenic when administered to humans, and thus would have been advantageous for clinical applications. The motivation to produce less immunogenic antibodies was expressly provided by Bickel et al., who state at p. 124 that genetically engineering monoclonal antibodies, such as by humanization, may facilitate their use as neurodiagnostic or therapeutic agents in humans. This teaching is echoed by both Becker and by Ladner, who expressly

disclose that human monoclonal antibodies and genetically engineered antibodies, such as single chain antibodies, are particularly useful for clinical use due to reduced immunogenicity. As for the functional properties of the claimed antibodies (i.e., inhibition of β-amyloid and/or maintenance of β-amyloid solubility), it is noted that the instant specification discloses no more than the combined teachings of the above references.

iv) Claims 177, 210-213, 215-217, 219-223 and 225-227 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al. (*J. Neuropathol Exp Neurol.* 1994 Jul; 53(4):377-383), as evidenced by Hanan and Solomon (*Amyloid: Int J Exp Clin Invest.* 1996; 3:130-133) and Bacskai et al. (*Nat Med.* 2001; 7(3): 369-372), in view of EP 0613 007 A2 to Becker et al. (published 08/31/1994).

Claims 210, 215 and dependant claims thereof recite a pharmaceutical composition comprising a genetically-engineered antibody, or fragment thereof, that inhibits aggregation of β-amyloid or maintains the solubility of soluble β-amyloid to an extent at least as great as that obtainable with antibody AMY-33, and claims 219, 225 and dependent claims thereof recite a pharmaceutical composition comprising a genetically-engineered antibody, or fragment thereof, that disaggregates an aggregate of β-amyloid, wherein the genetically-engineered antibody is derived from a monoclonal antibody obtainable using a peptide consisting of residues 1-28 of β-amyloid as an immunogen or one that recognizes an epitope within residues 1-28 of β-amyloid, and wherein said antibody or fragment is not conjugated with a detectable moiety. Claims

212, 222 and dependent claims thereof are further limited to a human monoclonal antibody.

Walker et al. teach that in Alzheimer's disease and other degenerative disorders of the brain, β-amyloid (Aβ) is deposited in senile plaques, diffusely in the neuropil, and in the walls of cerebral blood vessels (see p. 377, left column). Walker demonstrates the ability of the monoclonal antibody 10D5, and Fab fragments thereof, to label β-amyloid plaques in the brain tissue of aged monkeys. 10D5 antibody or Fab fragments (neither of which were conjugated to a detectable moiety) were administered to the animals and binding of 10D5 was assessed in brain tissue samples 24 hours later (see Injection of Antibody and Immunohistochemistry on p. 378). Walker teaches that 10D5 antibody can selectively bind to cerebral Aβ. Walker therefore suggests that antibodies such as 10D5 may be employed to deliver therapeutic agents directly to Aβ in the brain, such as for the treatment of β-amyloidoses or Alzheimer's, or, in combination with imaging technologies such as PET or SPECT, to diagnose β-amyloidoses in living subjects (see p. 381 2nd paragraph, and p. 382, last paragraph). Walker does caution that a leukocytic reaction in response to administration of the antibody is of concern for clinical application (p. 382, last paragraph). In spite of this, however, Walker notes that *in vivo* localization and binding to Aβ, such as with Aβ-specific antibodies, has considerable potential for delivering therapeutic agents that could prevent or reverse Aβ deposition in the brains of patients with cerebrovascular amyloidosis or Alzheimer's disease (see p. 382, last paragraph).

As evidenced by Hanan and Solomon, the 10D5 antibody was raised against the peptide consisting of Aβ 1-28 (see p. 131, under "Antibodies") and recognizes an epitope within Aβ 1-28 (see Abstract). In fact, Walker teaches that 10D5 recognizes an epitope within Aβ 1-16 (see p. 377, 2nd column, 3rd paragraph). Hanan and Solomon evidence that 10D5 is more effective than AMY-33 in inhibiting the aggregation of β-amyloid (see p. 132 and Figure 1). Additionally, Bacskai et al. demonstrate that *in vivo* administration of the 10D5 antibody, even for diagnostic purposes such as *in vivo* imaging, results in reduction of brain amyloid deposits in aged PDAPP transgenic mice (an animal model of Alzheimer's disease). See, for example, Figures 2 and 5 and p. 371, 1st paragraph. Thus, Bacskai evidences that the 10D5 antibody, even when conjugated to another molecule, is capable of disaggregating an aggregate of β-amyloid. Thus, as evidenced by both Hanan and Solomon and by Bacskai et al., the 10D5 antibody inherently possesses the ability to inhibit soluble β-amyloid aggregation and disaggregate aggregated β-amyloid, both *in vitro* and *in vivo*. See MPEP § 2112 (II), which states, "there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure *at the time of the invention*, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003)."

The difference, therefore, between the prior art teachings of Walker and the instant invention is that Walker does not teach that the antibody is a genetically-engineered antibody such as a single chain antibody.

Becker et al. teach that Alzheimer's disease is characterized by amyloid plaques and neurofibrillary tangles, wherein β-amyloid peptide is regarded to be the major constituent of the amyloid plaque deposits (see column 1). Becker also notes that β-amyloid peptide can be neurotoxic to neurons (see column 1, lines 30-46). Becker therefore suggests that inhibition of β-amyloid-mediated neurotoxicity would be therapeutically beneficial for the treatment of Alzheimer's disease, and describes assays that can be used for determining appropriate inhibitors, such as anti-β-amyloid antibodies. Becker teaches that antibodies specific for β-amyloid peptide can be used in diagnostics, therapeutics, or in diagnostic/therapeutic combinations in humans, such as for the treatment of Alzheimer's disease (see column 7, lines 39-52 and column 8, lines16-18). Pharmaceutical formulations comprising a pharmaceutically acceptable carrier and an anti-β-amyloid antibody are taught at column 8, lines 19-26 and 31-42.

Monoclonal antibodies derived from various species, including humans, are disclosed at column 6, lines 10-19. In this respect Becker teaches the use of anti-β-amyloid human monoclonal antibodies. One of the greatest deterrents to the clinical use of antibodies produced in non-human species, Becker remarks at column 6, lines 31-35, is the risk of hyperimmunogenicity in human subjects due to the presence of non-human constant regions in the antibodies. Therefore, genetically engineering the antibodies to retain epitope specificity but reduce immunogenicity (i.e., chimeric, humanized, or CDR-grafted antibodies) is desirable (column 6, line 35 – column 7, line 10). Further, Becker teaches single chain antibodies as another genetically engineered antibody for retaining the binding characteristics of the parental antibody while affording

a less immunogenic format (column 7, lines 11-25). Thus, the ordinarily skilled artisan would have recognized that engineered antibodies with reduced immunogenicity would address Walker's concerns about the potential for immunogenic reactions occurring with the clinical use of non-human monoclonal antibodies in humans.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to genetically engineer the 10D5 monoclonal antibody to create a less immunogenic antibody molecule, such as a single chain antibody, for use in therapeutic applications as taught by both Walker et al. and Becker et al. Similarly, it would have been obvious to make a human monoclonal anti-Aβ antibody, as taught by Becker, obtainable using a peptide consisting of residues 1-28 of Aβ because this was the immunogen used to produce the 10D5 antibody and commonly known and used in the art at the time of filing, and Walker demonstrates that this antibody binds specifically to brain amyloid deposits, thus evidencing the usefulness of antibodies obtained with this immunogen. Human monoclonal antibodies were known to be less immunogenic when administered to humans, and therefore would have been advantageous for clinical applications. The skilled artisan would have been motivated to make such changes because Walker teaches that the anti-β-amyloid 10D5 antibody could be used to deliver therapeutic agents to cerebral β-amyloid deposits, but notes that the mouse monoclonal antibody may have immunogenicity issues when used in humans. A 10D5 antibody conjugated to a therapeutic agent for delivery of such agents to β-amyloid deposits is distinct from an antibody conjugated to detectable moiety, because the therapeutic agent is not a detectable moiety as defined by the instant specification. Becker teaches

that immunogenicity of non-human anti-Aβ antibodies can be reduced whilst still retaining the epitope specificity of the parental antibody by antibody engineering techniques, such as by engineering single chain antibodies from the parental monoclonal antibody or by the use of human monoclonal antibodies. Because these antibody engineering techniques were well-known and established in the art at the time of filing, the artisan would have had a reasonable expectation that the production of genetically engineered antibodies for clinical applications in humans would have been successful. As noted and evidenced above, the 10D5 antibody taught by Walker inherently possesses the capacity to inhibit β-amyloid aggregation and/or disaggregate aggregated β-amyloid as instantly recited in the claims, and would still have been expected to possess such characteristics upon genetic engineering to produce a single chain antibody. Therefore, the combined teachings of the above references render obvious the presently recited invention of claims 177, 210-213, 215-217, 219-223 and 225-227.

(10) Response to Argument

i) Regarding the New Matter rejection of claims 177 and 210-218, at the paragraph spanning pages 14-15 Appellant asserts the specification does contain an assay for comparing the anti-aggregating abilities of candidate antibodies. Appellant notes that Figures 7A and 7B show the result of an assay that compares the anti-aggregating properties of AMY-33 and 6F/3D, and which assay may be used to compare any two antibodies.

Appellant's argument has been considered but is not persuasive. The aggregation assay disclosed in Example 2 and shown in Figures 7A and 7B was used to test whether the AMY-33 or 6F/3D antibodies could individually affect the aggregation of β-amyloid under different aggregating conditions (e.g., β-amyloid in the presence of heparan sulfate or metal ions zinc (Zn^{2+}) or aluminum (Al^{3+}), or β-amyloid alone), not explicitly to compare the antibodies' anti-aggregating properties to each other. Notably, the results of these tests are provided in separate figures for AMY-33 (Figure 7A) and 6F/3D (Figure 7B), evidencing that a direct comparison between the two antibodies was not intended by the disclosure. There is no mention, either explicitly or implicitly, that the assay described in Example 2 at columns 15-16 (or under "Amyloid ELISA Assays" at column 13, lines 20-50) should be used to compare candidate antibodies directly to AMY-33. Furthermore, 6F/3D was not shown to inhibit aggregation of β-amyloid or maintains the solubility of soluble beta-amyloid *to an extent at least as great as that obtainable with antibody AMY-33,* as recited in the claims.

At page 16-17, Appellant asserts that the present specification contains the generic concept of all antibodies that bind β-amyloid and inhibit aggregation or cause disaggregation, which includes the entire range of anti-aggregating activity, and the specific anti-aggregating activity shown in Figure 7A for AMY-33. Thus, Appellant argues, there is implicit or inherent support the range beginning at the activity of AMY-33 shown in Figure 7A and higher, and points to MPEP 2163.05 III, relating to range limitations, for support.

Appellant's arguments have been considered but are not persuasive. The instant situation is dissimilar to the example noted by Appellant at MPEP 2163.05 III, which describes a specific broad numerical range (i.e., "a range of 25%-60%") and specific examples within the range (i.e., "36%" and "50%"), because in the present case, the recitation of an antibody with anti-aggregating properties "at least as great as that obtainable with antibody AMY-33" has no upper limit to the claimed antibody's anti-aggregating ability, as opposed to the defined range of "between 35% and 60%" which falls within the disclosed 25%-60% range of the noted example. The fact pattern is more similar to the other example provided in the *In re Wertheim* case at MPEP 2163.05 III, which notes that "[a] corresponding new claim limitation to "at least 35%" did not meet the description requirement because the phrase "at least" had no upper limit and caused the claim to read literally on embodiments outside the "25% to 60%" range" (emphasis added). Because there is no upper limit to the presently recited anti-aggregating property that is "at least as great as that obtainable with antibody AMY-33", the range of potential antibodies encompassed by the claims includes those having far better anti-aggregating properties than AMY-33. Thus, the genus of anti-aggregating anti-beta-amyloid antibodies and a single species within this genus (AMY-33) does not support the uppermost, unlimited range of antibodies having a degree of functional anti-aggregating ability meeting or exceeding that of AMY-33.

The instant fact pattern most closely resembles a genus/subgenus relationship, wherein all antibodies that bind β-amyloid and inhibit β-amyloid aggregation or cause disaggregation represent a genus, and antibodies capable of inhibiting aggregation

better than AMY-33 represent a subgenus. Thus, Appellant has effectively narrowed the scope of the claimed subject matter to focus on antibodies have a specific degree of functional ability. However, MPEP 2163.05 II states:

The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph.

See also *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) ("Whatever may be the viability of an inductive-deductive approach to arriving at a claimed subgenus, it cannot be said that such a subgenus is necessarily described by a genus encompassing it and a species upon which it reads." (emphasis added)). Each case must be decided on its own facts in terms of what is reasonably communicated to those skilled in the art. *In re Wilder*, 736 F.2d 1516, 1520, 222 USPQ 369, 372 (Fed. Cir. 1984).

The added limitation that the claimed antibody or antigen-binding fragment "inhibits aggregation of beta-amyloid or maintains the solubility of soluble beta-amyloid to an extent at least as great as that obtainable with antibody AMY-33" implies a subgenus of antibodies having a specific degree of functional ability. The recitation of "at least as" in particular implies a functional activity that includes those antibodies with equivalent or greater functional activity than that of AMY-33. However, the instant specification only provides one antibody with the exact activity of AMY-33. The specification as originally filed therefore did not explicitly or implicitly indicate this subgenus of antibodies as part of the invention. Furthermore, as previously noted by Appellant, not all antibodies that recognize an epitope within residues 1-28 of β-amyloid peptide are capable of inhibiting aggregation of β-amyloid and/or maintaining the solubility of soluble β-amyloid (see, for example, the Table provided by Appellant at p. 39 of the Appeal Brief). Therefore, based upon the art-recognized unpredictability of the ability of any anti-β-amyloid

antibody (even those which recognize an epitope within residues 1-28 of β-amyloid) to inhibit β-amyloid aggregation and/or maintain β-amyloid solubility, and the limited disclosure of only one antibody, AMY-33, that is capable of such inhibition, the skilled artisan would not recognize that Appellant reasonably provided an adequate written description of a subgenus of antibodies that meet or exceed the functional activity of the AMY-33 antibody.

ii) Regarding the Written Description rejection of claims 177 and 210-218, Appellant argues at p. 18 that Example 2 of the present specification provides support for classifying antibodies based upon a particular level of functional activity, as indicated by the results of the individual monoclonal antibody AMY-33 (which is noted as being effective at preventing self-aggregation of β-amyloid in the presence and absence of heparan sulfate) and 6F/3D (which is noted to be only partially effective in the presence of Zn^{2+} but otherwise ineffective under all other aggregating conditions) in a β-amyloid anti-aggregation assay.

Appellant's arguments have been fully considered but are not persuasive. The assay provided at Example 2 states that it "investigates the immunocomplexation effect on the in vitro aggregation of β-amyloid", wherein the "β-amyloid aggregation was followed by ELISA measurements using two different commercially available monoclonal antibodies raised against β-amyloid:…6F/3D…and mAb AMY 33" (see column 15, lines 24-38). The next paragraphs at column 15 go on to describe the aggregation of β-amyloid in the absence and presence of the antibodies and under

various aggregating conditions (heparan sulfate, metal ions), and the role that metal ions and particular residues within the amino acid sequence of β-amyloid play in contributing to aggregation of the β-amyloid molecule. Thus, the disclosure provides for a characterization of the factors that contribute to β-amyloid aggregation, and implies that the aggregation assay could be used to select anti-aggregating monoclonal antibodies. However, there is no explicit mention of classifying antibodies based upon their ability to inhibit β-amyloid aggregation under the different aggregating conditions. A skilled artisan would reasonably interpret the description of the effects of 6F/3D and AMY-33 on β-amyloid aggregation at column 15, lines 39-53, as merely relaying the results of the test assays, not as providing a framework by which other candidate antibodies should be compared and classified based upon their functional activity.

At p. 19, Appellant states that the claims previously read on all levels of functional activity (i.e., a genus that included AMY-33 and all other antibodies raised against the claimed immunogen or recognizing the claimed sequence), and then were amended to recite that the activity must be at least as great as that of AMY-33. Appellant thus contends that because Appellant was in possession of the entire genus prior to the amendment, so Appellant is in possession of the subgenus of antibodies. At pp. 20-23, Appellant points to Example 13 of the Written Description Guidelines, which is directed to an antibody that binds to antigen X. Appellant notes that antibody technology at the time of filing was well-developed and mature. Appellant asserts that there is not a substantive difference between the present situation and the claim of Example 13, and that the present claims differ from Example 13 only in that they are

narrower in scope, but this fact does not make the present claims lose written description support. The instant claims require a screen of a genus of antibodies to select only those that inhibit β-amyloid aggregation or maintain β-amyloid solubility, then a step to compare the degree of inhibition/solubility maintenance with that of known and available antibody AMY-33. Appellant thus contends that the subgenus of antibodies of the present claims is supported for the same reason that the genus of Example 13 is supported.

Appellant's arguments have been fully considered but are not found persuasive. In view of MPEP 2163.05 II noted above, which states that "[t]he introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph", the amendments to the claims have created a subgenus of genetically-engineered and human antibodies having specific functional requirements that are no longer supported by the present specification as filed. The examiner agrees that Appellant has written description support for a genus of antibodies that bind to β-amyloid peptide, consistent with Example 13 provided in the training materials. But here the similarity between Example 13, which recites a claim drawn to "an isolated antibody capable of binding to antigen X", and the instant claims ends.

The current situation is one of an antibody molecule having a particular functional activity in addition to a binding requirement, and is therefore more similar to Example 10, claim 3, of the written description guidelines, which is directed to a protein variant

having a particular function. In Example 10, the specification disclosed only one species within the claimed genus – similar to the present situation. The guidelines' analysis of claim 3 determined that further testing would be required to identify which proteins had the desired functional activity, and that based on the lack of knowledge and predictability in the art, those of ordinary skill in the art would not conclude that the Appellant was in possession of the claimed genus of proteins based on the disclosure of the single species. That is, with respect to claim 3, the specification failed to satisfy the written description requirement.

As Appellant has indicated, one of skill in the art would have to perform not one but two selection steps to arrive at the claimed subgenus of antibodies: 1) a screening for antibodies that inhibit β-amyloid aggregation or maintain β-amyloid solubility, and 2) a comparison to the known inhibitory activity of AMY-33. The examiner agrees that the general knowledge in the art would have allowed the skilled artisan to produce generic antibodies to a given protein, such as β-amyloid. However, the instantly claimed antibodies go beyond a simple binding requirement; the present antibodies are mandated not only to bind β-amyloid, but also to inhibit its aggregation or maintain its solubility to an extent at least as great as that of antibody AMY-33, and be either genetically-engineered or human antibodies. The totality of the structural and functional requirements of the present antibody thus amounts to a particular subgenus within the genus of anti-aggregating anti-β-amyloid antibodies for which Appellant has only demonstrated one species, AMY-33, which itself does not even fulfill all the requirements of the claims because it is not "genetically engineered" as defined by the

claim limitations nor is it a human monoclonal antibody. In this respect, Appellant has not provided even one species within the presently claimed subgenus of genetically-engineered or human monoclonal antibodies which meet or exceed AMY-33 functionality, or even the broader genus of genetically engineered or human monoclonal anti-aggregating β-amyloid antibodies, for which the skilled artisan could look to for support.

Moreover, as demonstrated by the Table provided by Appellant as evidence at p. 39 of the Appeal Brief, not all antibodies that recognize an epitope within residues 1-28 of β-amyloid are capable of inhibiting β-amyloid aggregation (see, for example, the monoclonal antibodies 2H3, 1C2, 266, and 6F/3D). Given the unpredictability of producing anti-β-amyloid antibodies that have the ability to inhibit β-amyloid aggregation, those of ordinary skill in the art would not conclude that Appellant was in possession of the claimed genus of antibodies based on the limited disclosure in the instant specification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483 (BPAI 1993). In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence. Finally, in *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326, 56 USPQ2d 1481, 1486 (Fed Cir. 2000), the court

noted that with respect to *In re Ruschig* 379 F.2d 990, 154 USPQ 118 (CCPA 1967) that "*Ruschig* makes clear that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say "here is my invention". In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure". In the instant case, the "forest" of antibodies that bind β-amyloid have been disclosed, but the "tree" of an antibody that exceeds the anti-aggregating activity of AMY-33 has not been so disclosed. Accordingly, the specification fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph.

iii) Regarding the rejection of claims 177, 210-213 and 215-217 under 35 U.S.C. 103 as being obvious over Bickel, Solomon (2002), Becker and Ladner, Appellant argues at pp. 25-27 (part A) that it would not have been obvious to genetically engineer antibody AMY-33. In particular, Appellant asserts that the only specific utility taught by Bickel is a diagnostic utility, but all of the rejected claims have a "wherein" clause specifying that the antibody or fragment "is not conjugated with a detectable moiety." According to Appellant, Bickel does not suggest or enable any use for which a detectable moiety would not be necessary. Regarding the therapeutic use of monoclonal antibodies taught in Bickel, Appellant asserts that the statements in the last paragraph of Bickel are generically applicable to any antibody that one wishes to use as neurodiagnostic or therapeutic agents in humans, and do not suggest that AMY-33 has any properties that would make it useful as a therapeutic agent. There is no enabling

disclosure in Bickel, Appellant argues, for any kind of therapeutic use for AMY-33, because the only disclosed *in vivo* use for this antibody that is taught or suggested by Bickel is as a diagnostic agent after it has been modified and detectably labeled. Thus, Appellant asserts that one of ordinary skill in the art would not be motivated by Solomon (2002), Becker or Ladner to genetically engineer AMY-33 so as to make a pharmaceutical formulation with a genetically engineered AMY-33 that does not have a detectable marker attached to the antibody.

Appellant's arguments have been fully considered but they are not persuasive. Bickel does indeed suggest that the AMY-33 antibody should be used *in vivo* diagnostically because of the impressive ability of the antibody to recognize and target β-amyloid in cerebral amyloid deposits. While Bickel detectably labeled the AMY-33 antibody in his studies, one of ordinary skill in the art would recognize that not all antibodies used in diagnostic applications are required as a rule to be detectably labeled. In fact, Ladner explicitly teaches that a genetically-engineered single chain antibody "can be utilized by itself, in detectably labeled form, in immobilized form, or conjugated to drugs or other appropriate therapeutic agents, in diagnostic, imaging, biosensors, purifications, and therapeutic uses and compositions. Essentially all uses envisioned for antibodies or for variable region fragments thereof can be considered for the molecules of the present invention." (emphasis added) See column 11, lines 27-34. In other words, Ladner discloses that non-detectably labeled single chain antibodies may be used both diagnostically and therapeutically. Further, Becker teaches that anti-β-amyloid antibodies may be used in diagnostics, therapeutics, or diagnostic/therapeutic

combinations via the *in vivo* administration of the antibodies to humans (column 7, lines 39-49). In such diagnostic or diagnostic/therapeutic combinations, diagnosis could, for example, be achieved by administering an anti-β-amyloid antibody to a subject and then monitoring a particular response, such as the level of β-amyloid (free or immunocomplexed with the antibody) in a blood, cerebrospinal fluid (CSF), or brain tissue sample prior to and following administration of the antibody. The antibody in this situation would not need to be conjugated to a detectable moiety (a labeled secondary antibody could be used instead), and if it were used for a diagnostic/therapeutic combination application, the anti-β-amyloid antibody would preferably not be detectably labeled.

Contrary to Appellant's arguments, there is nothing described in Bickel to in any way suggest that AMY-33 is inappropriate for use therapeutically. However, even assuming that the only utility suggested and enabled by Bickel (as alleged by Appellant) is that of diagnosis, then in view of Becker and Ladner it would still have been obvious to the ordinarily skilled artisan to genetically engineer a non-detectably labeled AMY-33 antibody for diagnostic purposes. However, as Appellant notes, Bickel also generically suggests that humanized monoclonal antibodies could be used therapeutically, and Becker teaches the use of pharmaceutical formulations comprising anti-β-amyloid antibodies (particularly those which have been engineered to be less immunogenic, such as humanized or single chain antibodies), for the treatment of Alzheimer's disease. Because it was known at the time of filing that brain amyloid deposits are a major pathological component of Alzheimer's disease, an antibody that specifically and reliably

targets amyloid plaques in the brain would have been deemed valuable as a therapeutic entity. The ability of an antibody to bind to its target antigen with a high degree of specificity is paramount for both *in vivo* diagnostic and therapeutic applications. Therefore, in view of the teachings of Becker, the ordinarily skilled artisan would have also been motivated to use a genetically-engineered, less-immunogenic AMY-33 antibody in a pharmaceutical formulation because of the demonstrated ability of AMY-33 to target amyloid plaques in brain tissue. Again, it is noted that the instant specification discloses no more than what is provided in the prior art references with respect to actual therapeutic use of such antibodies.

At pp. 27-29 (part B) of the appeal brief, Appellant argues that the use of a post-filing date publication (Solomon (2002)) to establish obviousness is in error. According to Appellant, the inherent characteristic of AMY-33 (i.e., the ability to inhibit β-amyloid deposition) was not known at the time of the effective filing date of the present application. Appellant therefore argues that obviousness cannot be predicated on what is unknown, and cites case law in support of this statement. In particular, Appellant asserts that the claims are not directed to a single identified antibody, that is, they are not directed to a genetically engineered AMY-33 but a genetically engineered antibody that has been selected for certain properties. Even though such properties may have been inherent, Appellant argues that these properties were unknown at the time of filing, and thus the reliance on the present specification and post-filing art to establish obviousness was improper.

Appellant's arguments have been carefully considered but they are not persuasive. In the first place, neither the Solomon (2002) reference nor the present disclosure were used to establish obviousness, but merely to evidence that the anti-aggregating property of the instantly claimed antibody is indeed inherent to the prior art AMY-33 antibody. See MPEP 2112. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Secondly, the basis of the rejection with respect to the obviousness of genetically engineering the AMY-33 antibody has nothing to do with whether or not it was known at the time of filing that AMY-33 had anti-aggregating properties. Selection of AMY-33 was motivated by other distinct factors altogether, as discussed above. See MPEP 2144 IV, which states:

> The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings."); *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991).

In the instant case, Appellant has recognized that certain antibodies, such as the anti-β-amyloid antibody AMY-33, are capable of inhibiting aggregation of β-amyloid, and

therefore proposes genetically-engineering such selected antibodies for use in therapeutic compositions. However, the prior art references of Bickel, Becker and Ladner have similarly recognized the usefulness of genetically engineering an anti-β-amyloid antibody, and in particular AMY-33, and also arrive at the claimed invention but from a different path.

Finally, while the scope of the presently claimed invention may indeed be broader than a single genetically-engineered antibody, there is no reason why a single antibody, and in particular a genetically engineered AMY-33 antibody, does not meet the limitations of the claims. As noted by Appellant in section ii above, the genus of presently claimed antibodies encompasses, as a representative species, a genetically-engineered AMY-33. Because a genetically-engineered AMY-33 antibody provides for all of the structural and functional limitations of the claimed antibody, the presently recited invention is rendered obvious in view of the combined teachings of Bickel, Becker and Ladner.

iv) Regarding the rejection of claims 177, 210-213, 215-217, 219-223 and 225-227 as being obvious over Walker, Hanan, Bacskai and Becker, Appellant urges that claims 219-223 and 225-227 are separately patentably from claims 177, 210-213 and 215-217, and therefore argues them independently in section D. Appellant indicates that sections A, B and C are applicable to all claims.

In section A (pp. 29-31), Appellant argues that it would not have been obvious to genetically engineer antibody 10D5. According to Appellant, Walker does not teach any

therapeutic use for antibody 10D5. Appellant asserts that while Walker suggests that there may be a therapeutic utility for an anti-β-amyloid antibody to deliver therapeutic agents to the brain of a patient, Walker does not teach that any such therapeutic agents exist. And even if they did exist, Appellant argues that Walker does not teach that antibody 10D5, when bound to such therapeutic agents, would still bind β-amyloid *in vivo*. Appellant contends that Walker provides no motivation to humanize antibody 10D5 or make it into a single chain antibody, and that Becker only suggests doing so with an antibody known to have some type of therapeutic or other *in vivo* utility. Further, Appellant argues that the only utility for antibody 10D5 taught by Walker is a diagnostic utility in combination with imaging technology, which would require labeled antibodies and the present claims exclude labeled antibodies. While the experiments of Walker do not use labeled antibodies, Appellant notes, this is only because they were able to remove the brains of the test monkeys and then label brain sections with a secondary labeled antibody, which Appellant states is "obviously not possible for diagnostic use of such antibodies in humans."

Appellant's arguments have been fully considered but are not persuasive. It is unclear how the teachings of Walker at p. 381 and 382 can be interpreted as anything other than a clear suggestion that anti-β-amyloid antibodies, such as 10D5, could be used to deliver therapeutic agents directly to β-amyloid (also called Aβ by Walker) in the brain. Appellant recognizes this suggestion too, and admits at p. 30 of the appeal brief that "…Walker suggests that there may be therapeutic utility for an antibody that can bind to β-amyloid in the brain in order to deliver therapeutic agents that could prevent or

reverse β-amyloid deposition in the brains of patients with cerebral vascular amyloidosis or Alzheimer's disease…" Whether or not Walker provides any actual therapeutic agents that could be delivered via such a mechanism is therefore irrelevant, because it is the proposed idea to *use* an anti-Aβ antibody as a means to deliver any appropriate therapeutic agent that is important. This suggestion, along with the teachings of Becker indicating that mouse monoclonal antibodies have the potential to elicit undesirable immunogenic reactions when used in humans, would have provided sufficient motivation for the artisan of ordinary skill to develop a less-immunogenic antibody that could be used for delivery of therapeutic agents to amyloid deposits in the brain.

Further, the ordinarily skilled artisan would have had no reason to doubt that such an antibody, once coupled to its appropriate therapeutic agent, would not be capable of binding to its intended target *in vivo*. At the time of filing, conjugation of antibodies to various other molecules, including detectable labels, peptides, polymers, and other agents, was well-known and established in the art. See, for example, Ladner et al. (of record and noted above), who indicates that antibody fragments (such as single chain antibodies) can be detectably labeled or "conjugated to drugs or other appropriate therapeutic agents" (column 11, lines 27-34). Were any antibody to be found incapable of binding its specific antigen due to the coupling process, it would not have been considered for use by the skilled artisan and would consequently have fallen outside the scope of Walker's proposed delivery antibody-therapeutic agent conjugate, which *requires* that the antibody specifically bind Aβ in the brain. Thus, based upon the suggestion of Walker and the teachings of Becker, the ordinary skilled artisan would

have arrived at a genetically-engineered 10D5 antibody capable of being coupled to a therapeutic agent, which conjugated antibody (which is not detectably labeled) could then be used in the treatment of cerebral amyloidosis or Alzheimer's disease.

Regardless, even assuming *arguendo* that the only utility taught by Walker is a diagnostic one, as noted above, one of skill in the art would have recognized that it is not essential that diagnostic antibodies be coupled to a detectable label. There is nothing to prevent the skilled artisan from administering a non-labeled anti-β-amyloid antibody to subject, retrieving a fluid or tissue sample from the subject, and then determining a level of β-amyloid (or β-amyloid immunocomplexed with the administered antibody) in the sample using a labeled secondary antibody, as was performed by Walker. The ordinary skilled artisan would of course have recognized that removal of person's entire brain would be unacceptable and, clearly, preposterous for diagnostic purposes, and therefore would have appreciated suitable alternatives for such diagnostic procedures, including the use of blood, CSF or brain tissue samples. Thus, it would have been possible to use a non-detectably labeled anti-Aβ antibody diagnostically *in vivo* in humans. It is critical to remember that the instant claims are directed to compositions, not therapeutic methods. In the phrase “therapeutic composition”, the word “therapeutic” is an intended use. An intended use does not carry patentable weight in prior art rejections. The prior art composition simply must not be inconsistent with the intended use, and that is certainly at least the case here. Therefore, when the prior art suggests the same compositions for another purpose as in this case, the prior art renders the instant claims obvious.

At section B (pp. 31-33), Appellant again asserts that the use of a post-filing date publication to establish obviousness is in error. Appellant argues that the allegedly inherent characteristics of the 10D5 antibody to inhibit β-amyloid deposition and disaggregate an aggregate of β-amyloid were not known at the time of the effective filing date of the present application. Again, Appellant cites case law indicating that "obviousness cannot be predicated on what is unknown." According to Appellant, the present claims are not directed to a genetically engineered 10D5 antibody, but to a genetically engineered antibody that has been selected for certain properties. Thus, the reliance on post-filing art to establish obviousness was improper, argues Appellant.

Appellant's arguments have been taken into consideration but they are not persuasive. As discussed above with the Walker/Solomon(2002)/Becker/Ladner rejection, the post-filing Hanan and Bacskai references were not provided to establish the obviousness of genetically engineering the 10D5 antibody, but merely to evidence that the 10D5 antibody inherently possessed the functional characteristics recited in the claims and thus met all of the limitations of the claimed antibody. In other words, these references are not necessary for establishing obviousness of the claimed invention, and are thus listed only as evidentiary references. The use of a post-filing reference(s) to establish inherency is not only permissible, but it is the examiner's duty to establish that the necessary features as claimed were necessarily present or inherent in the prior art product. See MPEP 2112, which states:

> "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the

> applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original).
>
> The express, implicit, and inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103. "The inherent teaching of a prior art reference, a question of fact, arises both in the context of anticipation and obviousness." *In re Napier*, 55 F.3d 610, 613, 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) (affirmed a 35 U.S.C. 103 rejection based in part on inherent disclosure in one of the references). See also *In re Grasselli*, 713 F.2d 731, 739, 218 USPQ 769, 775 (Fed. Cir. 1983). (emphasis added)
>
> "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). (emphasis added)

The broadest reasonable interpretation of the claims encompasses any genetically engineered anti-β-amyloid antibody that is capable of inhibiting aggregation of β-amyloid or maintaining solubility of soluble β-amyloid to an extent at least as great as that of AMY-33, or is capable of disaggregating an aggregate of β-amyloid, and is obtained by genetically engineering the DNA encoding a monoclonal antibody that is raised against residues 1-28 of β-amyloid or recognizes an epitope with residues 1-28 of β-amyloid and itself is similarly capable of such anti-aggregation/disaggregation activities. The 10D5 antibody meets all of the structural and functional limitations of the aforementioned monoclonal antibody as taught by Walker and as evidenced the Hanan and Bacskai references. Accordingly, a genetically engineered 10D5 antibody would be considered a species within the broadly claimed genus of genetically engineered antibodies which renders the instantly recited genus obvious.

The reasoning to select 10D5 for genetic engineering is distinct from the selection process described by Appellant. In the instant case, Appellant has recognized that certain antibodies, such as the anti-β-amyloid antibody AMY-33, are capable of inhibiting aggregation of β-amyloid, and therefore proposes genetically-engineering such selected antibodies for use in therapeutic compositions. However, the prior art references of Walker and Becker have recognized the usefulness of genetically engineering another anti-β-amyloid antibody, 10D5 (which inherently possesses all of the functional properties instantly claimed), for use in therapeutic applications as a delivery molecule, and therefore also arrive at the claimed invention but from a different path. The instantly rejected claims are product claims, not methods of producing said product as in claims 214, 218, 224 and 228, which notably are not included in this rejection. Therefore, how the antibody was selected for subsequent genetic engineering is not relevant here, because such limitations are not recited in the rejected product claims.

In section C (pp. 33-37), Appellant asserts that it would not have been obvious at the time the invention was made that antibody 10D5 possessed the claimed properties. Appellant argues that skilled artisans following the literature published since the filing of the instant application are aware that not all antibodies raised against β-amyloid will necessarily have the property of inhibiting aggregation of β-amyloid or maintaining β-amyloid solubility to an extent at least as great as that obtainable with antibody AMY-33 or the property of disaggregating an aggregate of β-amyloid. The specification clearly states, Appellant notes, that antibodies having the desired properties must be selected.

Appellant points to the Table at p. 39, attesting that while AMY-33 and eight other antibodies that bind to an epitope between residues 1 and 7 of β-amyloid have shown positive results in a disaggregation assay, the remaining several antibodies which recognized an epitope in Aβ 1-28 had negative results for disaggregation of Aβ. C-terminally directed antibodies (those directed to an epitope between residues 33 to 42) also showed negative results for inhibiting aggregation and/or disaggregating Aβ. Appellant also points to the Solomon (2002) reference, which according to Appellant confirms the fact that antibodies raised against the first 28 amino acids of β-amyloid do not necessarily have anti-aggregating properties, including solubilization of existing β-amyloid aggregates and inhibition of β-amyloid aggregation. A very specific epitope within 1-28 is required.

Further, Appellant contends that the present claims only read on antibodies that have a substantial amount of inhibiting activity (i.e., "as least as great as that obtainable with the antibody AMY-33"), and while the 10D5 antibody does inherently have the properties require for an antibody of the present invention, this fact was unknown and would not have been obvious at the time of filing. Appellant argues that not only were these properties unknown, but they were unobvious and unpredictable. Antibodies must be screened for the inhibiting or disaggregating properties required by the claims, and it would not have been obvious that 10D5 had such properties. Appellant therefore asserts that the unexpected property of inhibiting aggregation of β-amyloid and causing disaggregation of β-amyloid rebuts any case of *prima facie* obviousness.

Appellant's arguments have been fully considered but they are not deemed persuasive. Again it is emphasized that the Hanan and Bacskai references were not used to establish the obviousness of genetically engineering the 10D5 antibody, but only to evidence that the instantly claimed properties (inhibition of β-amyloid aggregation, maintaining solubility of soluble β-amyloid, disaggregating amyloid aggregates) were in fact inherently present in the 10D5 antibody such that it meets the recited limitations of the claimed antibody. Significantly, however, the reasoning and motivation to select the 10D5 antibody and genetically engineer it for therapeutic or diagnostic use is distinct from the reasoning put forth in the present disclosure, but this does not mean that the presently claimed invention is nonobvious. The claimed composition comprising a genetically engineered anti-Aβ antibody is quite broad, and thus any genetically-engineered antibody meeting the functional and loose structural requirements of the claims would render obvious the instant invention. The 10D5 antibody, and in particular a genetically engineered 10D5 antibody, does just that. There is nothing recited in the rejected claims that indicates that the antibodies must first be selected for specific properties prior to use in the claimed composition. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Regarding the data in the Table presently by Appellant, the examiner notes that all of the antibodies raised against *an immunogen consisting of a peptide consisting of residues 1-28 of β-amyloid* (as recited in the claims) were capable of disaggregating an

amyloid aggregate and/or preventing aggregation of β-amyloid *in vitro*. Thus, as recited by the claims and evidenced by the Table, any antibody raised against Aβ 1-28 could be reasonably predicted to be capable of at least inhibiting β-amyloid aggregation, and potentially also of disaggregating amyloid aggregates (no data for AMY-33 is provided for such a property). Notably, the 2H3 antibody referred to by Appellant was raised against Aβ 1-12, and therefore falls outside the scope of some of the instant claims. Secondly, the examiner notes that a column representing the ability of any of these antibodies to maintain the solubility of soluble β-amyloid (which is the other important property recited in the claims) is completely absent from the Table. Without such information, therefore, it is improper to conclude that antibodies raised against Aβ 1-28 or recognizing an epitope with Aβ 1-28 (or any anti-Aβ antibody for that matter) do not necessarily have the property of maintaining the solubility of soluble β-amyloid. It is possible, for example, that all anti-Aβ antibodies possess this property, albeit to a greater or lesser extent than the AMY-33 antibody.

Importantly, it is noted that with respect to the ability of antibodies to inhibit β-amyloid aggregation or disaggregate aggregated β-amyloid peptide as defined by their ability to recognize a particular epitope with β-amyloid, the instant application discloses little more that what was known and recognized in the prior art. There is no indication in the instant specification that Appellant set out to determine which epitope of the β-amyloid peptide would be the most effective for producing anti-aggregating antibodies. Appellant purchased two commercially-available antibody, AMY-33 and 6F/3D, and

used them in assays for measuring β-amyloid aggregation under different aggregating conditions. There is no indication in the present specification, for example, to first select specific antibodies having particular structural features, such as those that are raised against Aβ 1-28 and/or those which recognize an epitope within Aβ 1-28, screen the antibodies for their ability to inhibit aggregation or disaggregate aggregates, and then to compare those activities to those of AMY-33. And there is no evidence in the present specification of any antibody that is capable of disaggregating a previously existing aggregate of β-amyloid peptide. In this respect, Appellant has disclosed no more that what is provided in the prior art.

In any case, the 10D5 antibody meets the limitations of both being raised against a peptide consisting of Aβ 1-28 and recognizing an epitope within Aβ 1-28, as well as being evidenced to inhibit β-amyloid aggregation and disaggregate amyloid aggregates. There is nothing recited in the claims indicating that the antibody must first be screened for such properties, and even if there were, such would be considered a product-by-process limitation. Even if these limitations were present, it is noted that a product made by any other process renders a product-by-process claim unpatentable. See *In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983) and In re Thorpe, 777 F.2d 695, 227 USPQ 964 (Fed. Cir. 1985). Again, whether or not the anti-aggregating/disaggregating properties of the 10D5 antibody were unknown or unexpected at the time of time of filing is irrelevant, because the selection of the 10D5 antibody was based upon its impressive ability to target β-amyloid deposits in the brain, thus making it a good candidate for delivery of therapeutic agents to cerebral amyloid

plaques. Genetically engineering 10D5 to make it less immunogenic for use in humans would have therefore been obvious, based upon the combined teachings of Walker and Becker.

And finally in section D (pp. 37-38), Appellant asserts that the compositions of claims 219-223 and 225-227 have additional particularly unexpected properties. Appellant notes that claims 219-228 all require that the antibody disaggregate an aggregated β-amyloid, which activity is even more selective than inhibition of amyloid aggregation. According to Appellant, antibodies that cause disaggregation are even rarer than antibodies that inhibit aggregation (as seen in the Table at p. 39), and thus urges that these claims should be considered separately and independently free of the rejection of record.

Appellant's argument has been considered but is not persuasive. As noted above, there is no evidence in the present specification of any antibody that is capable of disaggregating an aggregate of β-amyloid peptide. In this respect, Appellant has disclosed no more that what is provided in the prior art. Therefore, if Appellant truly believes that the disaggregating property of such antibodies renders them separate and distinct from those antibodies which merely inhibit β-amyloid aggregation or maintain β-amyloid solubility, and in view of Appellant's insistence that such disaggregating antibodies are "rare" and therefore more unpredictable to obtain than other inhibitory antibodies, then it may be justifiable to revisit the matter of written description of the claimed disaggregating antibodies.

Regardless, the 10D5 antibody inherently possesses the property of being capable of disaggregating aggregated β-amyloid as admitted by Appellant at p. 36, bottom paragraph, and therefore a genetically-engineered 10D5 antibody renders the presently claimed invention obvious.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/KIMBERLY A BALLARD/

Kimberly A. Ballard, Ph.D.

Examiner, Art Unit 1649

Conferees:

/Elizabeth C. Kemmerer/

Elizabeth C. Kemmerer, Ph.D.

Primary Examiner, Art Unit 1646

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649